REMARKS

Claims 18, 20, 26, 27, and 28 are pending in this application and are all amended. Claims 19, 21, 24 and 25 are canceled with this amendment. Claims 1-17 were previously canceled. Claims 22, 23 and 29-34 were withdrawn without prejudice pursuant to the restriction requirement.

Claims 18 and 26-28 were amended to specify that micelles are mixed micelles of retinoic acid and nonionic surfactant. This amendment is supported by the description "*a nonionic surfactant, such as ... polyoxyethylene (20) sorbitan monooleate (Tween 80), is added along with retinoic acid. Tween 80, together with retinoic acid, forms mixed micelles*" at lines 14-17 on page 11 of the specification.

Claims 18 and 20 were amended to specify that the mixed micelles are coated with calcium carbonate in accordance with the election of the invention of Group I in response to the restriction requirement.

Claim Rejections -- 35 USC § 112

Claim 20 was rejected under 35 U.S.C. 112, first paragraph. Applicants have changed the range of the molar ratio in claim 1 from 1:0 to 1:1.0 to 1:0.01 to 1.0. Table 1 supports this amendment on page 17 of the specification, which specifically cites this molar ratio. Applicants respectfully submit that this rejection has been overcome.

Claim Objection -- 37 CFR § 1.75

Claims 24-25 were objected to under 37 CFR 1.75 as being a substantial duplicate of claim 18. Applicants have canceled claims 24 and 25. Therefore, Applicant submits that the objection under 37 CFR 1.75 has been overcome.

Claim Rejections -- 35 USC § Sec. 103(a)

Claims 18-21 and 24-28 were rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/096396 in view of Yamaguchi et al. (March 2002) and the Merck Index. U.S. Patent Application Publication 20004/0185113 is cited by the Examiner as an English language translation of WO 02/096396.

WO02/096369 (US2004/0185113 A1) discloses drug-encapsulating inorganic microparticles and a production method thereof. The microparticles disclosed in WO02/096369 comprise a biologically active substance coated with calcium carbonate (see claims 1 and 6 of US2004/0185113 A1). The production method of the microparticles comprises the steps of 1) preparing an aqueous solution of a calcium salt; 2) adding a biologically active substance into the aqueous solution; and 3) adding a carbonate into the mixed solution to encapsulating the biologically active substance with calcium carbonate (see claim 12).

WO02/096369 describes that this method can produce microparticles having an average particle size of 10 nm to 100 μm (see paragraph [0024]). However, WO02/096369 fails to disclose any example of an actual product of microparticles having an average particle size of 5 to 106.4 nm.

WO02/096369 describes that a surfactant may be added into the reaction solution to prevent the aggregation of the microparticles (see paragraph [0023]). However, WO02/096369 does not specify the type of surfactant, nor the time at which a surfactant is added.

Yamaguchi et al. (The Journal of Pharmaceutical Science and Technology, March 2002, 1-2, Vol.62, Supplement) discloses retinoic acid nanoparticles and a production method thereof. The nanoparticles disclosed in Yamaguchi et al. comprise spherical micelles of retinoic acid coated with calcium carbonate (see "Objective"). The

production method of the nanoparticles comprises the steps of 1) forming micelles of retinoic acid in aqueous solution; and 2) adding $CaCl_2$ and $NaCO_3$ into the aqueous solution (see "Experimental methods").

The retinoic acid nanoparticles have a diameter of about 125-164 nm (see "Results and Discussion").

The Merck Index (The Merck Index, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ, page 1404, entry no. 8333 (retinoic acid), 1996) discloses general information about retinoic acid.

The claimed inventions in amended claims 18 and 26-28 differ from the inventions of WO02/096369 and Yamaguchi et al. in that i) nanoparticles comprise a nonionic surfactant; and ii) nanoparticles have an average particle size of 5 to 106.4 nm.

As described in the specification of the present application, upon coating micelles of retinoic acid with an inorganic salt (calcium carbonate), there is a problem of aggregation of micelles of retinoic acid. To avoid this problem, it is proposed in the present invention that micelles of retinoic acid are produced as mixed micelles of retinoic acid and nonionic surfactant. In this regard, the specification of the present application describes as follows:

> "*The surface of the micelle is negatively charged and readily adsorbs (binds to) divalent metal ion…replacing sodium ion. Since the divalent metal ion is more tightly adsorbed (bound) to the micelles than is the sodium ion, the micelles having the divalent metal ions adsorbed on them have more stable surface charge, so that they become insoluble in water and precipitate. The precipitated particles aggregate into large clusters…To prevent aggregation of the charged particles, a nonionic surfactant…is added along with retinoic acid.*" (page 11 lines 6-17 of the specification)

In this regard, it is important to use a nonionic surfactant rather than an ionic surfactant. For example, if the micelles are prepared as mixed micelles of retinoic acid and cationic surfactant, the cationic surfactant reacts with carboxylic groups of retinoic acid, and thus the micelles become insoluble in water and precipitate. Therefore, it is

necessary to use a nonionic surfactant rather than an ionic surfactant in order to prepare the claimed retinoic acid nanoparticles having an average particles size of 5 nm to 106.4 nm.

In addition, it is important to form mixed micelles of retinoic acid and nonionic surfactant by adding a nonionic surfactant before adding calcium halide or acetate (Ca^{2+}). Once micelles of retinoic acid are coated with Ca^{2+}, the micelles become insoluble in water and aggregate into large clusters (page 11 lines 3-8 of the specification). These large clusters cannot disintegrate into individual micelles by the addition of a nonionic surfactant. Therefore, it is necessary to add a nonionic surfactant before adding calcium halide or acetate (Ca^{2+}) in order to prepare the claimed retinoic acid nanoparticles having an average particles size of 5 nm to 106.4 nm.

On the other hand, although WO02/096369 discloses the use of a surfactant to prevent the aggregation of microparticles, WO02/096369 fails to disclose the use of nonionic surfactant as the surfactant and the time at which a surfactant is added. Yamaguchi et al. discloses neither the above problem associated with the aggregation of micelles nor the use of a surfactant for avoiding this problem.

As mentioned above, it is possible to produce retinoic acid nanoparticles having an average particles size of 5 to 106.4 nm by adding a nonionic surfactant before adding calcium halide or acetate (Ca^{2+}) to form mixed micelles of retinoic acid and nonionic surfactant. However, it is not described in WO02/096369 and Yamaguchi et al. that a nonionic surfactant is added before adding calcium halide or acetate (Ca^{2+}). Therefore, the skilled person would not be able to produce retinoic acid nanoparticles comprising nonionic surfactant and having an average particles size of 5 to 106.4 nm based on the disclosures of WO02/096369, Yamaguchi et al. and The Merck Index. In fact, nanoparticles having an average particles size of 5 to 106.4 nm cannot be produced in WO02/096369 and Yamaguchi et al.

Therefore, Applicant submits that the claimed inventions in amended claims 18 and 26-28 are not obvious over the cited WO02/096369, Yamaguchi et al. and The Merck Index, either taken alone or in combination.

Claim Rejections – Provisional Nonstatutory Obvious-Type Double Patenting

Claims 18-21 and 24-28 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/595,412. Applicants are hereby submitting a terminal disclaimer with regard to the copending application, which they submit overcomes this rejection.

CONCLUSION

If the Examiner has any questions, he is respectfully requested to contact the undersigned. The Commissioner is hereby authorized to charge any additional fees, or to credit any overpayment, to Deposit Account No. 50-3195.

Respectfully submitted,

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Appendix:
Terminal Disclaimer